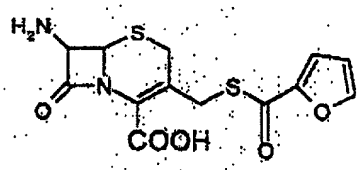
AN IMPROVED SYNTHESIS OF CEFTIOFUR INTERMEDIATE

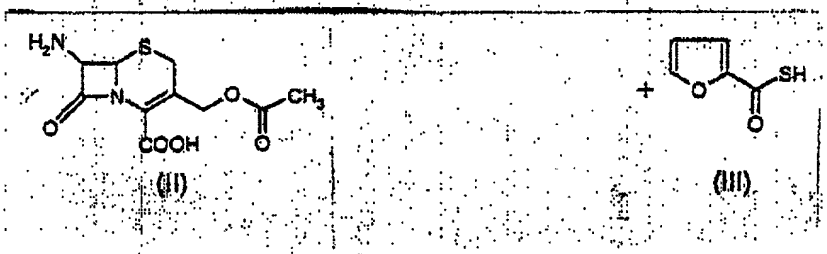
FIELD OF THE INVENTION

The present invention discloses an improved process for the preparation of 7-amino-3 -[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid represented by formula (I)



(I)

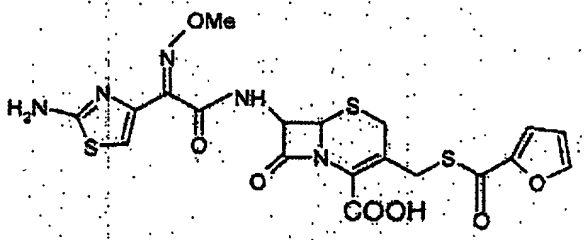
by the condensation of 7-amino cephalosporanic acid (7-ACA) represented by formula (II) with furyl-2-carbonylthiol represented by formula (III) using borontrifluoride as condensing agent.



(II) (III)

BACKGROUND OF THE INVENTION

Ceftiofur is the generic name given to compound of formula (IV)



(IV)

Ceftiofur acid, its alkali metal, alkaline earth metal and amines salts were reported for the first time in US patent no. 4464367. The ceftiofur is a condensation product of 7-ACA with furyl-2-carbonylthiol and 2-(2-amino thiazol-4-yl)-2-methoxyimino)

acetic acid at its 3 and 7 positions respectively. 7-amino-3 - [2-furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid represented by formula (I) is the key intermediate which decides the quality and overall yield of the process for making ceftiofur.

There are very few methods reported in the literature for the synthesis of 7-amino-3 - [2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid (I). The first report for the synthesis of this intermediate appeared in the US patent No. 4464367, wherein the method used for the preparation of the compound of Formula (I) was followed from a reference from the journal of Antibiotics 27,573-8,(1974) .This reference is about the condensation of 7 - aminocephalosporanic acid and sodium thiofuroate carried out at a pH of 6.4 using phosphate buffer .The reaction time is very long by following this tedious method and a yield is of 47% is reported for the final product. These limitations make this process unfavorable for commercial exploitation. Another method was disclosed in WO patent 87/01117 which is also merely an extension of the above-mentioned US patent. The condensation was effected by reaction of sodium thiofuroate and 7-ACA at a temperature of 65^0C in an aqueous medium at a pH of 6.4. Cephalosporins are known to decompose at high temperature and moreover using this process, the reaction is not completed and yields are also very poor (about 45% and in addition, the reaction takes longer time, for example, even after several hours the reaction is incomplete).

Looking at all these problems, a method for the condensation under non-aqueous conditions was reported in US patent no. 5387679, where condensation of 7-ACA with heterocyclic thiols in the presence of complex of borontriflouride with dialkyl carbonate was carried out to provide intermediates which are used in the synthesis of cephalosporin antibiotics.

When the process of US patent No. 5387679 is applied for the condensation of 7-ACA and furyl-2-carbonylthiol, the reaction mixture obtained is associated with several impurities, which could not be separated even during the final purification step. Later on, after several experimentation, the applicant found that the stability of furyl-2-carbonylthiol isolated in solid form is not encouraging. Further, this problem

is encountered because furyl-2-carbonylthiol belongs to the class of heterocyclic thioacids and not heterocyclic thiol. The behavior of the reaction is not similar for the thioacids as it was for thiols thereby disallowing the conditions of the US patent No. 5387679 to be used in the present invention to achieve the final result.

In order to overcome this problem, the applicant provides for the first time an improved process for condensing 7-ACA with furyl-2-carbonylthiol which is generated and used *in situ* in the presence of borontriflouride in a gaseous state or its solution in an organic solvent to obtain compound of formula (I). This process gives desired product of formula (I) in excellent yield (90-95%) and high purity (98-99%).

OBJECTS OF THE INVENTION

The primary object of the invention is to provide an improved and commercially viable efficient process for preparing 7-amino-3-[2-(furylcarbonyl)thiomethyl]-3-cephem-4-carboxylic acid (I), as an intermediate for ceftiofur.

Another object of the invention is to use furyl-2-carbonylthiol in situ without isolating it.

Yet another objective of this invention is to provide a process which will give high yield and purity of the required product.

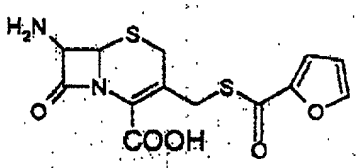
Still another object of the invention is to provide the use of boron trifluoride in gaseous state or its solution in an organic solvent for carrying out the condensation reaction at low temperature which are convenient for commercial production.

SUMMARY OF THE INVENTION

To meet the above objectives, the present invention provides a process for the preparation of 3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid (I) by the condensation of 7-aminocephalosporanic acid (II) with furyl-2-carbonylthiol (III) in the presence of borontrifluoride at a temperature range of 20°-50°C in an organic solvent. This process gives high yields and excellent purity.

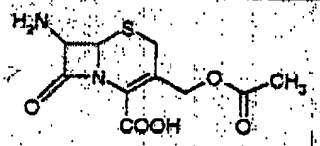
DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a process for the preparation of 3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid represented by formula (I),

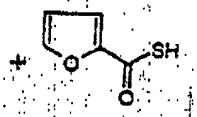


(I)

the said process comprising the steps of condensing 7-aminocephalosporanic acid (II) with furyl-2-carbonylthiol (III) in the presence of borontrifluoride at 20°-50°C in an organic solvent and isolating the compound of formula (I).

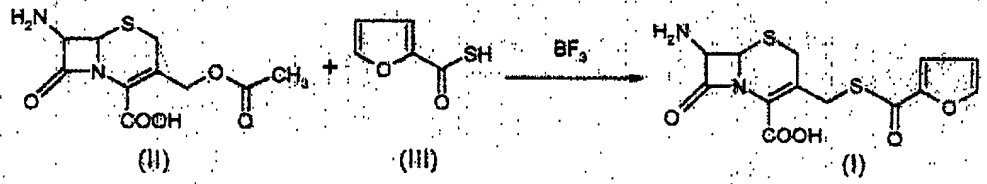


(II)



(III)

In an embodiment of the present invention, the sequence of the present reaction is shown herebelow:



(II) (III) (I)

An embodiment of the present invention provides a temperature range of 30°-35°C for performing the condensation reaction.

Another embodiment of the present invention provides a pH range of 3-4 and preferably 3.45-3.55 for the precipitation of the solid from the solution.

Yet another embodiment of the present invention provides the drying of the precipitated solid at a temperature range of 40°-45°C under vacuum.

One embodiment of the present invention provides the use of furyl-2-carbonylthiol in situ as a solution in an organic solvent.

Another embodiment of the present invention provides the use of organic solvent in the condensation reaction selected from group consisting of ethyl acetate, methyl acetate, propyl acetate, dichloromethane, toluene, diethyl ether, diisopropyl ether and/or mixture thereof.

One another embodiment of the present invention provides the use of base to adjust the pH of the reaction mixture is selected from a group consisting of ammonium hydroxide, sodium hydroxide or sodium carbonate.

Yet another embodiment of the present invention provides use of condensing agent borontriflouride in its gaseous form or its solution in an organic solvent.

Still yet another embodiment of the present invention the required product is obtained by precipitation and followed by filtration.

The invention is illustrated with following examples, which should not be construed as limiting the scope of the invention.

Example –I

7-Amino - 3-(2-furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid (I)

Charge sodium sulfide (54.6 g) in water (600ml) and furyl-2-carbonylchloride (50.0g) is added over a period of 60 minutes at a temperature of 20°C. Ethyl acetate is added to it and pH of the reaction mixture mass is adjusted to 1.0. The organic layer is separated, dried over anhydrous sodium sulphate, filtered to get furyl-2-carbonylthiol in ethyl acetate.

In an another flask ethylacetate (350ml) is charged, boron trifluoride (124.0g) gas is purged into it. 7-Amino-cephalosporanic acid (91.0 g) is added at 10.0^{0}C into the solution of borontrifluoride followed by the addition of furyl-2-carbonylthiol solution in ethylacetate (prepared above). The reaction is completed by stirring for 4 -5 hr at 30-40^{0}C. After completion of the reaction, the mixture is poured into ice cold water. The pH of the solution is adjusted to 3.45-3.55 by addition of ammonium hydroxide. The solid precipitated is filtered and washed with mixture of water and ethylacetate to get 7-amino - 3-(2-furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid (I, 110.0g) with a purity of 98-99 % by HPLC.

Example –II

7-Amino - 3-(2-furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid (I)

Charge sodium sulfide (36.4 g) in water (400ml) and furyl-2-carbonylchloride (33.3.0g) is added to it over a period of 60 minutes at a temperature of 20^{0}C. Ethyl acetate is added to it and pH of the reaction mixture is adjusted to 1.0. The organic layer is separated, dried over anhydrous sodium sulphate, filtered to get furyl-2-carbonylthiol in ethyl acetate.

In an another flask acetonitrile (350ml) is charged, boron trifluoride gas (85.0g) is purged into it. 7-Amino-cephalosporanic acid (60.6 g) is added at 10.0^{0}C into the solution of borontrifluoride, followed by the addition of furyl-2-carbonylthiol solution in ethylacetate (prepared above). The reaction is completed by stirring for 5 -6 hr at 30-40^{0}C. After completion ofthe reaction, the mixture is poured into ice cold water. The pH of the solution is adjusted to 3.45-3.55 by addition ammonium hydroxide. The solid precipitated is filtered and washed with mixture of water and acetonitrile to get 7-amino - 3-(2-furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid (I, 69.0g) with a purity of 97-98 % by HPLC.

Example –III

7-Amino - 3-(2-furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid (I)

Charge sodium sulfide (54.6 g) in water (600ml) and furyl-2-carbonylchloride (50.0g) is added to it over a period of 60 minutes at a temperature of 20^{0}C. Ethyl acetate is

added to it and pH of the mixture is adjusted to 1.0 by adding hydrochloric acid. The organic layer is separated, dried over anhydrous sodium sulphate, filtered to get furyl-2-carbonylthiol in ethyl acetate.

In an another flask containing acetonitrile (350ml) is added 7-Amino-cephalosporanic acid (91.0 g) at room temperature followed by addition of 45-48% solution of boron trifluoride etherate (275.5ml) at a temperature of 10.0^0C. To this added furyl-2-carbonylthiol solution in ethylacetate (prepared above) and the reaction is completed by stirring for 4 -5 hr at $40\text{-}50^0$C. After completion of the reaction, the mixture is poured into ice cold water. The pH of the solution is adjusted to 3.45-3.55 by addition of sodium carbonate solution . The solid precipitated is filtered and washed with mixture of water and ethylacetate to get 7-amino-3-(2-furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid (I, 104.0g) with a purity of 97-98 % by HPLC .